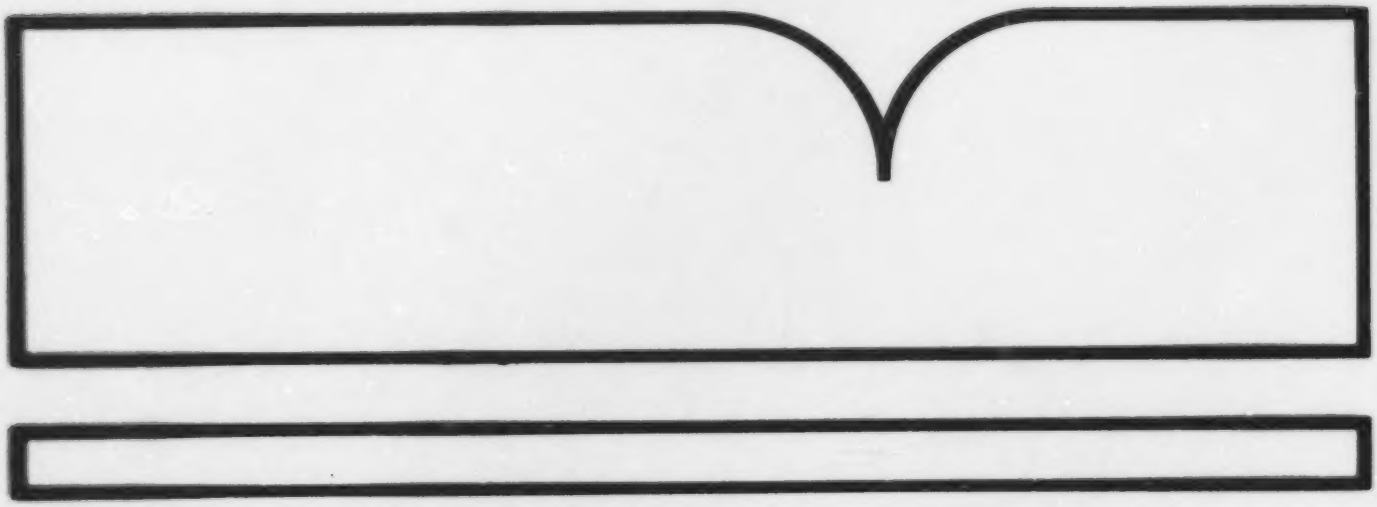
PB86-117835

Drinking Water Criteria Document for Ethylbenzene (Final Draft)

(U.S.) Environmental Protection Agency
Cincinnati, OH

Mar 85



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1.	2.
3. RECIPIENT'S ACCESSION NO. PB86 117835/AS	
SUBTITLE Drinking Water Criteria Document for Ethylbenzene	5. REPORT DATE 3/85
	6. PERFORMING ORGANIZATION CODE
AUTHOR(S) Environmental Protection Agency	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS U Environmental Protection Agency O. ce of Drinking Water (WH-550) 401 M St., S.W., Washington, D.C. 20460	13. TYPE OF REPORT AND PERIOD COVERED Scientific review
	14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on ethylbenzene. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of ethylbenzene
- Toxicokinetics and human exposure to ethylbenzene
- Health Effects of ethylbenzene in humans and animals
- Mechanisms of toxicity of ethylbenzene
- Quantification of toxicological effects of ethylbenzene

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Ethylbenzene properties Ethylbenzene exposure Ethylbenzene toxicity Drinking Water		

18. DISTRIBUTION STATEMENT OPEN	19. SECURITY CLASS (This Report) Non-sensitive	21. NO. OF PAGES 78
	20. SECURITY CLASS (This page) Non-sensitive	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-430
March, 1985

EPA-600/X-84-163-1

PB86-117835

EPA

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR ETHYLBENZENE

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

DRAFT: DO NOT CITE OR QUOTE

NOTICE

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical accuracy and policy implications.

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

DISCLAIMER

Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AVAILABILITY NOTICE

This draft document is for internal review and should not be released. For information contact Dr. Jerry F. Stara, Director, Environmental Criteria and Assessment Office, Cincinnati, OH (513/684-7531).

DOCUMENT DEVELOPMENT

William E. Pepelko, Ph.D., Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Helen H. Ball, Project Officer
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

John M. Becker, Ph.D.
Dipak K. Basu, Ph.D.
Michael W. Neal, Ph.D.
Patrick Durkin, Ph.D
Syracuse Research Corporation
Syracuse, New York
(Contract 68-03-3112)

Robert McGaughy, Ph.D.
Carcinogen Assessment Group
U.S. Environmental Protection Agency

Herbert H. Cornish, Ph.D.
830 W. Clark Road
Ypsilanti, MI 48197
(Contract 68-03-3224; Eastern Research Group)

Penelope A. Fenner-Crisp, Ph.D.
William Lappenbusch, Ph.D.
Office of Drinking Water
U.S. Environmental Protection Agency

Scientific Reviewers

Thomas J. Haley, Ph.D.
17 Becky's Rideaway
Pine Bluff, AK 71603
(Contract 68-03-3224; Eastern Research Group)

Editorial Reviewers

Erma Durden, B.S.
Judith Olsen, B.A.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Document Preparation

Technical Support Services Staff: C. Cooper, P. Daunt, C. Fessler, K. Mann, B. Zwayer, Environmental Criteria and Assessment Office, Cincinnati

TABLE OF CONTENTS

		Page
I.	EXECUTIVE SUMMARY	I-1
II.	GENERAL INFORMATION AND PROPERTIES	II-1
	STRUCTURE AND IDENTIFICATION	II-1
	PHYSICAL AND CHEMICAL PROPERTIES	II-1
	ENVIRONMENTAL FATE RELATED TO WATER	II-1
	SUMMARY	II-5
III.	TOXICOKINETICS	III-1
	ABSORPTION	III-1
	DISTRIBUTION	III-3
	BIOACCUMULATION AND RETENTION	III-3
	METABOLISM	III-5
	EXCRETION	III-11
	SUMMARY	III-12
IV.	HUMAN EXPOSURE	IV-1
	EXPOSURE ESTIMATION	IV-1
	Drinking Water	IV-1
	Diet	IV-3
	Air	IV-4
	SUMMARY	IV-6
	REFERENCES	IV-8
V.	HEALTH EFFECTS IN ANIMALS	V-1
	GENERAL TOXICITY	V-1
	Acute Toxicity	V-1
	Subchronic and Chronic Exposure	V-4
	TARGET ORGAN TOXICITY	V-6
	OTHER EFFECTS	V-9
	Carcinogenicity	V-9
	Mutagenicity	V-9
	Teratogenicity	V-10
	SUMMARY	V-11
VI.	HEALTH EFFECTS IN HUMANS	VI-1
	CLINICAL CASE STUDIES	VI-1
	EPIDEMIOLOGICAL STUDIES	VI-1
	HIGH RISK SUBPOPULATIONS	VI-2
	SUMMARY	VI-3

		Page
VII.	MECHANISMS OF TOXICITY.	VII-1
	SYNERGISTIC AND ANTAGONISTIC INTERACTIONS.	VII-2
	SUMMARY.	VII-3
VIII.	QUANTIFICATION OF TOXICOLOGICAL EFFECTS	VIII-1
	EXISTING STANDARDS AND CRITERIA.	VIII-3
	NONCARCINOGENIC EFFECTS	VIII-3
	QUANTIFICATION OF NONCARCINOGENIC EFFECTS	VIII-5
	1-Day HA.	VIII-5
	10-Day HA	VIII-6
	Lifetime AADI	VIII-6
	CARCINOGENIC EFFECTS	VIII-7
	QUANTIFICATION OF CARCINOGENIC EFFECTS	VIII-7
	SPECIAL CONSIDERATIONS	VIII-7
	Synergistic Effects	VIII-7
	High Risk Subpopulations.	VIII-8
	SUMMARY.	VIII-8
IX.	REFERENCES.	IX-1

LIST OF TABLES

No.	Title	Page
II-1	Physical Properties of Ethylbenzene	II-2
III-1	Metabolic Profile of Ethylbenzene Determined *In Vivo* and *In Vitro* in Rats and Dogs	III-7
IV-1	Estimated Respiratory Intake of Ethylbenzene.	IV-5
IV-2.	Estimated Intake of Ethylbenzene from the Environment by Adult Males in µg/kg/day	IV-7
V-1	Target Organ Toxicity of Ethylbenzene	V-7
VIII-1	Summary of Data Used to Derive HA and AADI.	VIII-9

LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
HA	Health advisory
LC_{50}	Concentration lethal to 50% of recipents
LD_{50}	Dose lethal to 50% of recipients
LOEL	Lowest-observed-effect level
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
TLV	Threshold limit value
v/v	Volume per volume
W	Watts

I. EXECUTIVE SUMMARY

Ethylbenzene is a colorless, flammable liquid that is slightly soluble in water. In aquatic media, ethylbenzene is not likely to undergo significant chemical or photochemical reactions. The two most likely mechanisms by which this compound may disappear or degrade from ambient aquatic media are volatility and biodegradation. This compound is likely to be significantly sorbed by particulate matters in water. Significant bioconcentration of this compound by aquatic species seems unlikely. Conventional municipal drinking water treatment processes may not remove ethylbenzene from influent water.

Ethylbenzene appears to be readily absorbed from the gastrointestinal tract, lungs and skin. Distribution appears to be throughout the body; however, because of its lipophilic nature, concentrations of ethylbenzene can be expected to be higher in adipose tissue. In laboratory animals, ethylbenzene is metabolized rapidly to methylphenylcarbinol glucuronide (30-35%), hippuric acid (30-55%), phenaceturic acid (10-20%) and other minor metabolites. Based on the detection of urinary metabolites, the metabolism of ethylbenzene in humans appears to be different from that of the laboratory animals. Mandelic acid and phenylglyoxylic acid accounts for 64 and 25%, respectively, of the absorbed ethylbenzene in humans, while both are minor metabolites in rats. Urinary excretion of oxidized metabolites of ethylbenzene is the predominant route of elimination.

SUMMARY OF HUMAN EXPOSURE TO BE PROVIDED BY SCIENCE AND TECHNOLOGY BRANCH

Ethylbenzene, having an oral LD_{50} of 3.5 g/kg in the rat, is not severely toxic after acute exposure. Acutely and chronically exposed animals develop liver and kidney pathologies and nervous system disorders. Following a 6-month oral exposure, no toxic effects were reported in rats receiving 13.6 and 136.0 mg ethylbenzene/kg bw/day. Slight effects were reported in rats treated by inhalation with 400 ppm ethylbenzene for 7 hours/day, 4-5 days/week for as many as 214 days (~113 mg/kg/day). Ethylbenzene vapor at 400 ppm, 7 hours/day, 5 days/week for 186 days caused no toxic effects in guinea pigs, rabbits and rhesus monkeys.

The carcinogenicity of ethylbenzene has not been adequately tested. In the limited number of assays with Salmonella typhimurium strains, ethylbenzene did not appear to be a mutagen. Ethylbenzene exposure prior to mating or during gestation did not increase the frequency of terata or cause embryotoxicity in rats or rabbits. A reduced number of live rabbit kits/litter was reported, but this was not regarded as ethylbenzene-induced because there was no dose-related trend.

Relatively little information is available regarding the human health effects of ethylbenzene. Ethylbenzene exposure at 100 ppm for 8 hours was reported to cause no toxic effects, but levels exceeding this caused fatigue, sleepiness, headache and mucous membrane irritation. Occupational exposure to ethylbenzene usually coincides with xylene exposure, and generally the health-related effects are attributed to xylene. Ethylbenzene is used in a purified form in the production of styrene, but data regarding health effects on workers exposed in this manner are not available.

The mechanism of ethylbenzene toxicity has not been precisely determined. At least some liver and kidney changes may be associated with the increased metabolism and excretion of the toxicant. Acute lethal effects may be due to pulmonary hemorrhage after endothelial irritation. Central nervous system effects, which may lead to death, may be attributable to accumulation of ethylbenzene in the myelin lipid and subsequent oxygen deprivation of the neurons.

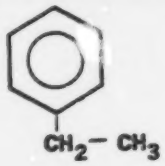
Based on the acute NOAEL of 100 ppm by inhalation in humans, the 1-day HA for a child and adult, and the 10-day HA for a child and adult were determined. The respective values were 21 and 73 mg/ℓ/day for the 1-day HA, and 2.1 and 7.3 mg/ℓ/day for the 10-day HA. Assuming that 136 mg/kg/day is a conservative NOAEL in the rat, the lifetime AADI was determined to be 3.4 mg/ℓ drinking water.

II. GENERAL INFORMATION AND PROPERTIES

Structure and Identification

The structure, molecular formula, molecular weight, Chemical Abstracts Service (CAS) Registry number, Registry of Toxic Effects of Chemical Substances (RTECS) number and common synonyms of ethylbenzene are listed below:

Structure:



Molecular formula: C_8H_{10}

Molecular weight: 106.18

CAS number: 100-41-4

RTECS number: DA0700000

Synonyms: Phenylethane, Ethylbenzol

Physical and Chemical Properties

Ethylbenzene is a colorless, flammable liquid with an aromatic odor. It is slightly soluble in water (152 mg/ℓ at 20°C) but miscible with many organic solvents (Verschueren, 1983). The taste threshold for ethylbenzene in water is 0.1 mg/ℓ (unspecified type, e.g., recognition, detection); the odor detection threshold is 0.2 mg/ℓ (Fazzalari, 1978). These and other physical properties of ethylbenzene are presented in Table II-1.

Environmental Fate Related to Water

No experimental data pertaining to the volatility of ethylbenzene from the aquatic phase could be found; however, an EXAMS model (Burns et al.,

TABLE II-1

Physical Properties of Ethylbenzene[a]

Property	Value
Boiling point, 760 torr:	136.2°C
Melting point:	-94.97°C
Specific gravity at 20°C:	0.867
Vapor pressure at 25.9°C:	10 mm[b]
Relative vapor density (air = 1):	3.66
Saturated concentration in air at 20°C:	40 g/m³
Conversion factor (at 20°C and 760 mm):	1 mg/m³ = 0.23 ppm
Log of the octanol/water partition coefficient:	3.15
Water solubility at 20°C:	152 mg/ℓ

[a]Source: Verschueren, 1983

[b]Sandmeyer, 1981

1981) predicted that the volatilization half-lives of ethylbenzene in a pond, eutrophic lake, oligotrophic lake and river would be 3.4, 11, 13 and 2.9 days, respectively. Input parameters for the simulation were taken from Mabey et al. (1981) and included the reaeration rate ratio (K_v^c/K_v^o = 0.489), and Henry's law constant (6.6x10^{-3} atm-m^3/mole), as well as other parameters listed in Table II-1.

The volatility of ethylbenzene has also been estimated by Lyman et al. (1982). Based on a calculated value of the relative liquid film coefficient, these authors estimated the half-life for evaporation of ethylbenzenes from water as 3.1 hours from a water depth of 1 m at a wind velocity of 3 m/second and water current of 1 m/second.

Both hydrolysis and photolysis of ethylbenzene are probably not significant processes in aquatic media (Mabey et al., 1981; Callahan et al., 1979). Similarly, on the basis of the oxidation rate constants for this compound with singlet oxygen (>>360 M^{-1} hr^{-1}) and peroxy radical (720 M^{-1} hr^{-1}) (Mabey et al., 1981) and the concentrations of singlet oxygen (10^{-12} M) and peroxy radicals (10^{-9} M) (Mill et al., 1982), oxidation of this chemical seems environmentally insignificant.

Ethylbenzene at an initial concentration of 11 ppb in river water was not removed (0% removal) at all by sand filtration (Verschueren, 1983). Activated carbon, on the other hand, reduced ethylbenzene concentration by ~84% from an influent concentration of 115 ppm to an effluent concentration of 18 ppm. No experimental value for the rate of sorption or sorption efficiency of this compound in suspended particulate matters in water sediment

could be found. An EXAMS model (Burns et al., 1981) predicted that the sediments of a pond, eutrophic lake, oligotrophic lake and river would sorb 48, 6.8, 10 and 42% of the ethylbenzene load, respectively. Input parameters were taken from Mabey et al. (1981) and included a sediment/water partition coefficient of 1100.

Ethylbenzene, at an initial concentration of 1.36 ppm (v/v), was shown to completely biodegrade (100%) in 8 days upon incubation with natural flora in the groundwater at 13°C in the presence of other components of a high-octane gasoline (100 ppm v/v) (Verschueren, 1983). With activated sludge treatment, ethylbenzene was shown to biodegrade. Thus, phenol-acclimated activated sludge removed 27% of theoretical oxygen demand in 3 days at an initial concentration of 500 ppm. Using the static-culture flask-screening procedure and settled domestic waste water as microbial inoculum, Tabak et al. (1981) demonstrated that 100% degradation of 5 ppm ethylbenzene occurred in 7 days. Similarly, Patterson and Kodukala (1981) demonstrated that 78-99% removal of ethylbenzene (initial concentration 45-882 ppb) occurred with activated sludge treatment of municipal and industrial effluents. Conventional municipal drinking water treatment processes, however, do not remove ethylbenzene (Verschueren, 1983).

Employing the correlation equation of Veith et al. (1979) and the low K_{ow} value of 3.15, the BCF for ethylbenzene is estimated to be ~146. From their experiments with clams, Tapes semidecussata, in a flowthrough system under natural environmental conditions, Nunes and Benville (1979) estimated the BCF of 4.7 for ethylbenzene in clam tissue. By comparison with the BCF values (10^3 to 10^6) for DDT and PCBs (Callahan et al., 1979) where

considerable bioconcentration of these chemicals are known to occur, the BCF value for ethylbenzene suggests that ethylbenzene is not likely to bioconcentrate substantially in aquatic species.

Summary

Ethylbenzene is a colorless, flammable liquid that is slightly soluble in water. In aquatic media, ethylbenzene is not likely to undergo significant chemical or photochemical reactions. Volatility and biodegradation are the two most likely mechanisms by which this compound may disappear or degrade from ambient aquatic media. This compound is likely to be significantly sorbed by particulate matters in water. Significant bioconcentration of this compound by aquatic species seems unlikely. The conventional municipal drinking water treatment processes may not remove ethylbenzene from influent water.

III. TOXICOKINETICS

Absorption

Pertinent data regarding the absorption of ethylbenzene from the gastrointestinal tract following oral ingestion could not be located in the available literature.

The absorption of ethylbenzene vapor by inhalation was studied in young (100-120 g) male Harlan-Wistar rats (Chin et al., 1980a). Radiolabeled (^{14}C-ring)ethylbenzene vapor was maintained at ~1 mg/ℓ (1000 mg/m^3) throughout a 6-hour exposure period by gas chromatographic monitoring at 15-minute intervals for the first hour and for 30-minute intervals thereafter. The absorbed dose of ethylbenzene was calculated as the quantity of chemical needed throughout the exposure period to maintain the constant chamber concentration. The mean quantity of ethylbenzene absorbed, based on three exposed rats, was 16 mg/rat during the 6-hour period. The authors reported that, assuming each 100 g rat inhaled 36 ℓ of air during 6 hours (0.1 ℓ/minute), the total inhaled dose would be 36 mg of ethylbenzene. Each rat absorbed ~16 mg of ethylbenzene; therefore, 44% absorption through the lungs was achieved. These authors failed to address the fact that rats also were exposed dermally to ethylbenzene during this study, so absorption rates by inhalation at this atmospheric concentration may be slightly overestimated.

Following an 8-hour inhalation experiment with 18 human volunteers exposed to ethylbenzene at 100, 187, 200 or 370 mg/m^3, the average percent of vapor absorbed through the respiratory tract was 64% (Bardodej and Bardodejova, 1970). The method by which this absorption coefficient was

was not explicated, but it was determined from average values at all exposure levels. This absorption coefficient of 64%, however, is comparable with the 44% in rats reported by Chin et al. (1980a).

Studies conducted by Tsuruta (1982) examined the percutaneous absorption of ethylbenzene through excised rat abdominal skin. Depilated skin (2.55 cm^2) was mounted in a glass diffusion cell, where 1 mℓ of pure ethylbenzene (>98%) was applied to the exterior. After 3-6 hours, the amount of ethylbenzene passing through the rat skin into the receiving chamber, which contained 0.9% NaCl, was determined. After 3 hours, 18.2 µg of ethylbenzene had penetrated the skin. Similarly, after 3.5, 4, 5 and 6 hours, 22.4, 31.8, 41.1 and 68.0 µg, respectively, had passed through the skin. A lag time of ~2 hours was determined for ethylbenzene to pass through the rat skin. Tsuruta (1982) reported a penetration rate of 0.993 nmoles/cm^2/minute (0.105 µg/cm^2/minute) of skin for the rat.

The absorption of ethylbenzene through the human skin was examined in seven male volunteers in two experiments (Dutkiewicz and Tyras, 1967). Absorption from an aqueous solution was determined by immersing one hand in a solution of ethylbenzene (109.3-113.9 or 147.5-162.0 mg/ℓ) for 1 hour, or both hands for 2 hours. Absorption of pure liquid ethylbenzene was determined by applying the compound, contained under a watchglass, to the forearm for 10 or 15 minutes. The average amount of absorbed ethylbenzene after immersing the hand in a 109.3-113.9 mg/ℓ solution was 39.2 mg, which was equivalent to 118 µg/cm^2/hour (1.97 µg/cm^2/minute) based on the surface area of the hands. Absorption from a more concentrated ethylbenzene solution (147.5-162.0 mg/ℓ) was increased to 70.7 mg or 215.7

μg/cm²/hour (3.6 μg/cm²/minute) when one hand was exposed. When both hands were immersed in ethylbenzene at a mean concentration of 142 mg/ℓ, the total ethylbenzene absorbed was 247.4 mg, but the absorption rate was decreased to 189.4 μg/cm²/hour (3.15 μg/cm²/minute). When liquid ethylbenzene was applied directly to an area (17.3 cm²) of the forearm, the average absorption rate was 22-33 mg/cm²/hour (~450 μg/cm²/minute). The amount of ethylbenzene absorbed in both experiments was measured as that quantity which was not recovered after washing the exposed skin at the end of the exposure period.

Distribution

Ethylbenzene (C^{14}-ring labeled) or metabolites determined 42 hours after a 6-hour inhalation exposure (1 mg ethylbenzene/ℓ) were distributed throughout the body in rats (Chin et al., 1980a). While low levels (<0.001% of absorbed dose) were detected in the thyroid, adrenal, blood cells, spleen, brain and bone marrow, higher levels were detected in the kidney (0.003%), lung (0.006%), adipose tissue (0.007%), digestive tract (0.008%), liver (0.014%) and the remaining carcass (0.160% of the 16 mg/rat absorbed dose). The tissue levels of ethylbenzene or metabolites detected 42 hours after exposure were lower than those actually achieved during or just after exposure because a majority of the compound was excreted from the body after 42 hours (Excretion Section).

Bioaccumulation and Retention

In a study using male Wistar rats treated at doses of 25, 100 or 200 ppm (108, 434 or 868 mg/m³) ethylbenzene (with simultaneous exposure to m-xylene) for 6 hours/day for 5 days, Elovaara et al. (1982) reported that

accumulation in the perirenal fat was exponentially related to the inhaled dose. Concentrations of ethylbenzene in the perirenal adipose tissue were ~0.2, 0.3 and slightly >1.0 μmole/g (0.02, 0.03 and 0.1 mg/g tissue) following exposure at 25, 100 or 200 ppm (108, 434 or 868 mg/m³) ethylbenzene (plus 75, 300 or 600 ppm m-xylene), respectively.

The accumulation and retention of ethylbenzene in the adipose tissue was examined in 12 male volunteers exposed to industrial xylene that contained 40.4% ethylbenzene (Engstrom and Bjurstrom, 1978). Exposure was at 100 ppm (435 mg/m³) for 30 minutes at rest, followed by three 30-minute intervals of work [50, 100 and 150 watts (W) respectively] during one experiment and at 200 ppm (870 mg/m³) for 30 minutes at rest and three, 30-minute intervals of work (50 W each) in the second experiment. (Work was done on a bicycle ergometer.) Adipose samples from the upper gluteal area were taken at 0.5, 2, 4 and 20-24 hours after final exposure. Body fat content of the men was determined by an underwater weighing technique. The uptake of ethylbenzene and xylene was directly related to the amount of body fat as well as to the exposure level. The mean concentration of ethylbenzene and xylene for all men exposed at 435 mg/m³ was 4.0, 6.0, 4.0 and 8.0 mg/kg adipose tissue (determined by gas chromatography) at 0.5, 2, 4 and 22 hours after exposure, respectively. The mean concentration in men exposed at 870 mg/m³ was 8.0, 9.0, 6.0 and 6.5 mg/kg adipose tissue at 0.5, 2, 4 and 22 hours after exposure, respectively. Based on the uptake of xylene and ethylbenzene, adipose samples and excretion data, the authors estimated that ~5% of the total uptake was retained in the adipose tissue 22 hours after exposure.

Metabolism

The proposed metabolism of ethylbenzene, determined in rats and rabbits and *in vitro*, is summarized in Figure III-1. In rats exposed to ethylbenzene by inhalation at ~1 mg/ℓ (1000 mg/m³) for 6 hours, six urinary metabolites were detected (Table III-1) (Chin et al., 1980b). Unfortunately, the metabolites were not chemically identified. These researchers recovered only three metabolites of ethylbenzene produced *in vitro* by rat liver. Ethylbenzene administered *in vitro* to rat hepatic microsomes resulted in differing metabolite profiles when the dose was altered (see Table III-1). A beagle dog exposed to 1000 mg/m³ for 3.5 hours excreted six metabolites as well, while dog liver *in vitro* produced four of the same and one additional metabolite. Chin et al. (1980b) emphasized the differences between metabolites produced *in vitro* versus *in vivo*, as well as differences in the amount and identity of metabolites between species.

In rabbits treated with aqueous ethylbenzene by stomach tube (~2.5 g/animal), the predominant step of metabolism was the alpha-hydroxylation to methylphenylcarbinol (Smith et al., 1954a). Both isomers of this metabolite were conjugated to glucuronide and excreted in the urine. Smith et al. (1954b) reported that ~32% of the 2.5 g ethylbenzene administered to each rabbit was collected in the urine as a glucuronide conjugate. The urinary glucuronide in rats was identified as methylphenylcarbinol-glucuronide (McMahon and Sullivan, 1966). These investigators reported that rabbits and rats produced methylphenylcarbinol, *in vivo*, as a urinary metabolite after intraperitoneal ethylbenzene treatment. Kiese and Lenk (1973) reported that ~31% of the intraperitoneally administered ethylbenzene was isolated from the urine as methylphenylcarbinol in treated rabbits. Methylphenylcarbinol

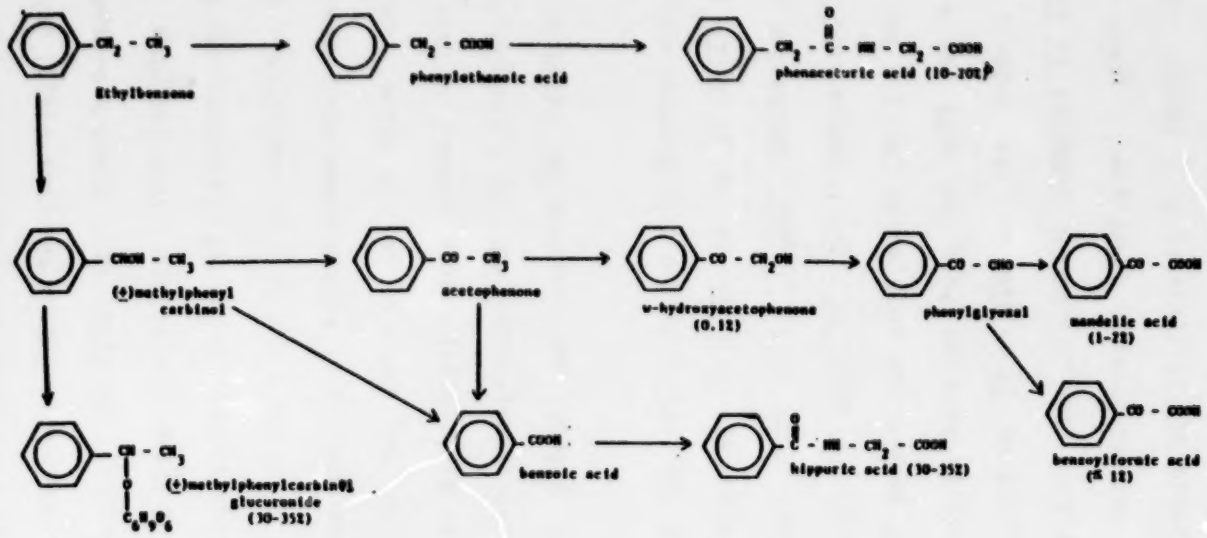


FIGURE III-1

Major Pathways of Ethylbenzene Metabolism in Laboratory Animals[a]

[a]Sources: El Masry et al., 1956; Williams, 1959; Kiese and Lenk, 1974; Sullivan et al., 1976

[b]Percent of absorbed dose excreted as urinary metabolite

TABLE III-1

Metabolic Profile of Ethylbenzene Determined *In Vivo* and *In Vitro* in Rats and Dogs[a]

Species	Test Method	Dose	Percent of Metabolites[b,c]						
			A	B	C	D	E	F	G
Rat (n = 3)	inhalation	1000 mg/m³ x 6 hours[d]	3.2	0.0	54.2	35.0	7.0	0.1	0.6
	in vitro	5 µg/ℓ	19.3	0.0	70.0	10.7	0.0	0.0	0.0
		50 µg/ℓ	46.8	0.0	45.1	8.1	0.0	0.0	0.0
Dog (n = 1)	inhalation	1000 mg/m³ x 3.5 hours[e]	1.2	4.7	25.0	51.8	10.4	0.0	5.9
	in vitro	10 µℓ	12.7	0.0	7.3	69.8	6.6	3.6	0.0

[a]Source: Chin et al., 1980b

[b]Percent of total radioactivity recovered as determined by column chromatography and scintillation counting.

[c]Metabolites were not chemically identified

[d]Reported to be ~20 µℓ (17 mg/animal) absorbed dose

[e]Reported to be ~50 µℓ (43 mg/animal) absorbed dose

was also produced *in vitro* by isolated rat liver microsomes, but at a slightly different isomer (D^+/L^-) ratio. *In vivo* in rats, ~90% of the hydroxylated metabolite occurred as the D^+-methylphenylcarbinol isomer, while *in vitro*, ~80% was metabolized to this isomer. Urinary hippuric acid and phenaceturic acid accounted for 31 and 10-20% of the administered (320 mg/kg by gavage) ethylbenzene, respectively (El Masry et al., 1956).

Minor metabolites of ethylbenzene identified in the urine of treated rats (Sullivan et al., 1976) and rabbits (Kiese and Lenk, 1974) included mandelic acid (1-2% of administered dose), benzoylformic acid (~1%), benzoic acid, and w-, p- and m-hydroxyacetophenones (~0.1% for each) (see Metabolism Section). Benzene ring-hydroxylated metabolites of ethylbenzene have been identified *in vitro* and *in vivo*, but represent an extremely small percentage of the administered ethylbenzene (Kiese and Lenk, 1974). Sullivan et al. (1976) reported that when ethylbenzene is metabolized to benzoic acid through acetophenonedemethylation, the liberated methyl group is oxidized and expired as carbon dioxide.

In human volunteers exposed to ethylbenzene vapor at 23, 43, 46 or 85 ppm (100, 187, 200 or 370 mg/m^3) for 8 hours, three urinary metabolites were identified (Bardodej and Bardodejova, 1970). Mandelic acid, unlike any of the animal models tested, was the major metabolite, accounting for 64% of the absorbed ethylbenzene. Similarly, urinary phenylglyoxylic acid (benzoylformic acid) accounted for 25% of the absorbed ethylbenzene in humans, while in animals it accounted for ~1% of the administered dose (Sullivan et al., 1976). Average methylphenylcarbinol excretion was ~5% of the absorbed dose among 18 male volunteers. Bardodej and Bardodejova (1970)

did not identify acetophenone or w-hydroxyacetophenone as urinary metabolites and reported that urinary hippuric acid and mercapturic acid levels were not elevated (sensitivity of test methods would not demonstrate change of <2%).

Urinary metabolites identified from tnree laboratory technicians exposed to 42 ppm ethylbenzene and another exposed to 34 ppm ethylbenzene were reported in an abstract by Hagemann and Angerer (1979) to be amygdalic acid, phenylglyoxylic acid and 2-ethylphenol. The workers were exposed for 8 hours, and the 24-hour urine samples were evaluated. Approximately 1.1-1.4% of the absorbed ethylbenzene was excreted as the hydroxylated aromatic ring metabolite, 2-ethylphenol (Angerer and Lehnert, 1979).

Molecular oxygen rather than oxygen from water appears to be the source of oxygen in the hydroxylation of ethylbenzene to methylphenylcarbinol (McMahon et al., 1969). Oxygenation occurred by frontside displacement or "insertion" with retention of the hydrogen atom to complete the hydroxylation reaction forming methylphenylcarbinol. Further oxygenation of methylphenylcarbinol at the alpha-carbon, forming acetophenone, has been reported during in vitro metabolism studies (Maylin et al., 1973), and benzoic acid and hippuric acid have been identified in vivo (El Masry et al., 1956; Sullivan et al., 1976). The metabolism of acetophenone to benzoic acid requires demethylation, and the removed methyl group is oxidized to CO_2 and exhaled (Sullivan et al., 1976).

Another route of metabolism is the w-hydroxylation of ethylbenzene to phenylethanoic acid (Williams, 1959). This intermediate is conjugated with glycine to form phenaceturic acid, which may account for up to 20% of the administered dose of ethylbenzene (El Masry et al., 1956).

Minor metabolic pathways of ethylbenzene were determined indirectly in rats by analysis of urine for hydroxylated metabolites (Bakke and Scheline, 1970). Male albino rats were maintained on a purified diet to establish normal urinary constituents before the administration of a single 100 mg ethylbenzene/kg dose by stomach tube. Urinary metabolites were collected for 48 hours subsequent to dosing. The urine was frozen during the collection procedure in order to minimize the evaporation of volatile metabolites. Quantitative and qualitative analysis for minor hydroxylated metabolites was performed using gas chromatography and flame ionization detection. Bakke and Scheline (1970) identified 1-phenylethanol, 2-phenylethanol (trace), and p-ethylphenol (0.2-0.4% of the administered dose). A suspected intermediate to mandelic acid formation, 1-phenyl-1,2-ethanediol, was not detected in the urine during this study. The formation of mandelic acid has, however, been shown to be a minor metabolic pathway in rats (Sullivan et al., 1976). Proceeding from methylphenylcarbinol (see Figure III-1), oxidation at the alpha- and w-carbon results in phenylglyoxal, which is further oxidized to mandelic acid and benzoylformic acid (Sullivan et al., 1976). Kiese and Lenk (1974) identified minute amounts of w-hydroxyacetophenone (0.11% of administered dose), an intermediate in the oxidation to mandelic acid.

The major metabolic pathways of ethylbenzene are through oxidation at the alpha or w-side-chain-carbons and hydroxylation of the aromatic-ring (Williams, 1959). Kaubisch et al. (1972), however, reported that rat liver microsomes metabolized ethylbenzene to 2- and 4-hydroxy ethylbenzene. Intermediates of these metabolites were suggested to be arene oxides of ethylbenzene. The hydroxyethylbenzenes accounted for ~2% of the metabolites in an in vitro microsome assay (Kaubisch et al., 1972). Bakke and Scheline (1970) reported that p-ethylphenol (4-hydroxyethylbenzene) accounted for 0.2-0.4% of the 100 mg/kg dose of ethylbenzene in treated rats. Kiese and Lenk (1974) reported that p- and m-hydroxyacetophenone amounted to 0.13 and 0.03% of the administered dose in intraperitoneally injected rabbits (0.9 g/animal) and suggested that hydroxylation of the aromatic ring occurred after acetophenone was metabolized from ethylbenzene.

Excretion

The elimination of ethylbenzene is primarily through urinary excretion of metabolites and appears to be quite rapid. The excretion of metabolites in rabbits was reported to be complete within 24 hours after dosing by gavage with 1.78 g of ethylbenzene/rabbit (El Masry et al., 1956).

Engstrom and Bjurstrom (1978) reported that <5% of the absorbed dose of ethylbenzene, following exposure at 870 $\mu g/m^3$ for 2 hours in 12 male volunteers, was retained in the body after 22 hours. This indicates rapid elimination. More than 90% of the ethylbenzene absorbed by four laboratory technicians exposed to 34 or 42 ppm for a working day was excreted in the urine within 24 hours (Hagemann and Angerer, 1979).

Summary

Absorption of ethylbenzene by inhalation and percutaneous injection has been studied using rats and human volunteers as subjects; however, absorption following oral ingestion has not been examined quantitatively. Retention of ethylbenzene after inhalation exposure was ~40-65%, with subsequent distribution apparently throughout the body (Chin et al., 1980a; Bardodej and Bardodejova, 1970). Retention time for ethylbenzene does not appear to be long; however, an estimated 5% of inhaled ethylbenzene (870 mg/m^3) was concentrated in adipose tissue 22 hours after exposure (Engstrom and Bjurstrom, 1978). Metabolism of ethylbenzene appears to be quite different between humans and the animal species tested. Major metabolites in humans, mandelic acid and phenylglyoxylic acid, are minor metabolites in rats and rabbits. Major metabolites in laboratory animals are methylphenylcarbinol glucuronide, hippuric acid and phenaceturic acid, none of which were detected in the urine of exposed humans. Ethylbenzene is metabolized rapidly and excreted almost exclusively in the urine in animals and humans.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as ethylbenzene from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to ethylbenzene is limited to drinking water, food, and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

In the Exposure Estimation Section of this chapter, available information is presented on the range of human exposure and intake for ethylbenzene from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary Section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. The data available for estimating daily intake of ethylbenzene from drinking water are limited. Two national scale Federal

surveys included ethylbenzene as an analyte: the National Organics Reconnaissance Survey (NORS) and the Groundwater Supply Survey (GWSS) Regional and State data on ethylbenzene contamination are also available.

In the NORS (U.S. EPA, 1975b) also conducted in 1974, ethylbenzene was detected, but not quantified, in 6 of the 10 cities examined. The six supplies with positive levels of ethylbenzene included one groundwater supply and five surface water supplies.

Conducted between December 1980 and December 1981, the GWSS involved the sampling of 945 water supply systems (U.S. EPA, 1983). Of the supplies, ~50% of the supplies were selected randomly while the remainder were chosen by the states as having a high potential for contamination. In the randomly selected sample, ethylbenzene was observed in 3 of 466 systems (0.64%); the quantitation limit was 0.5 µg/ℓ. Two of the three positive values obtained came from supplies serving <10,000 persons, and had values of 0.78 and 1.1 µg/ℓ. The third positive value, found in a supply serving >10,000 persons, was 0.74 µg/ℓ. In the non-random portion of the GWSS, ethylbenzene was detected in 3 of 479 systems sampled (0.6%). All three positives were from systems serving <10,000 people, and had values of 0.55, 0.87 and 0.95 µg/ℓ (quantitation limit 0.5 µg/ℓ).

Ethylbenzene was observed in the New Orleans Area Water Supply Study conducted in 1974 (U.S. EPA, 1975a). Ethylbenzene was found in all three water plants sampled in the New Orleans study, with maximum measured concentrations of 1.6, 1.8 and 2.3 µg/ℓ.

In a study conducted by the state of New York, between September 1980 and January 1981, ethylbenzene was observed in 1 of 57 groundwater supplies sampled at a concentration of 1 µg/ℓ. Ethylbenzene was not observed in any of nine surface water or three supplies with a mixed source of water (detection limit = 1 µg/ℓ) (Close et al., 1982).

The available data suggest that ethylbenzene is an infrequent contaminant of drinking water from groundwater, at least at levels >0.5 µg/ℓ. There are too few data to assess the frequency of occurrence of ethylbenzene in surface water supplies. It should be noted that ethylbenzene is a priority pollutant and has been indicated as being among the 25 most frequently found compounds in industrial and municipal discharges (Shackelford et al., 1981) and has been reported in ambient surface waters (Shackelford and Keith, 1976).

The levels of ethylbenzene observed in drinking water when it has been found are in the very low µg/ℓ range. Assuming that ethylbenzene is present at the highest concentration reported (i.e., 2.3 µg/ℓ in New Orleans) the daily intake for the 70 kg adult male consuming 2 ℓ of drinking water/day would be 4.6 µg/day or 6.6×10^{-2} µg/kg/day.

Diet. The data on ethylbenzene are insufficient for use in estimating dietary intake. Ethylbenzene is not included in the FDA Market Basket Surveys, nor were any comparable studies found in the literature. The only information on the occurrence of ethylbenzene in a food product is that of Kinlin et al. (1972) who reported ethylbenzene to be 1 of 227 organic compounds present in roasted filbert nuts; no quantitative data were given.

In the absence of adequate data, it is assumed that food is not a significant source of ethylbenzene.

Air. Brodzinsky and Singh (1982) have compiled available published and unpublished atmospheric data on volatile organic chemicals, including ethylbenzene, into a master file, and have subjected these data to statistical analysis. An assessment of the quality, reliability and representativeness of the data was also performed. Each data point was given a "quality code" based on either a quantitative assessment or on the authors own experience and judgment. Quality codes were: 1 = Excellent; 2 = Good; 3 = Acceptable; 4 = Questionable; and Z = Unable to assign quality.

Using data for quality codes 1-3, Brodzinsky and Singh (1982) calculated the following median concentrations of ethylbenzene: rural/remote areas, 2 $\mu g/m^3$ (11 observations); urban/suburban areas, 5.2 $\mu g/m^3$ (669 observations); and source dominated areas, 2.7 $\mu g/m^3$ (181 observations). The highest level of ethylbenzene, sampled in a source dominated area, measured 14,000 $\mu g/m^3$ (Oldham et al., 1979).

The daily respiratory intake of ethylbenzene from air was estimated using the assumptions presented in Table IV-I and the median and maximum levels for ethylbenzene reported above. The estimates in Table IV-I indicate that the daily ethylbenzene intake from air for adults exposed to the median levels ranges from 46-120 μg/day (0.7-1.7 μg/kg/day). In contrast, the intake calculated using the maximum level reported is ~320,000 μg/day (4600 μg/kg/day); few if any persons are believed to be exposed

TABLE IV-I

Estimated Respiratory Intake of Ethylbenzene

Location	Exposure ($\mu g/m^3$)	Intake	
		(μg/day)	(μg/kg/day)
Rural/remote	2.0	46.0	0.7
Urban/suburban	5.2	120	1.7
Source dominated	2.7	62.0	0.9
Maximum	14,000	320,000	4,600

Assumptions: 70 kg man, 23 m^3 of air inhaled/day (ICRP, 1975).

continually at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Summary

Table IV-II presents a general view of the total amount of ethylbenzene potentially received by a 70 kg adult male from air, food and drinking water. Three separate exposure levels in air, four exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to ethylbenzene at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The drinking water levels selected are representative of the range of values observed in the various Federal survey and state data. It is assumed that the 70 kg adult male consumes 2 ℓ of drinking water/day.

Because information available on the presence of ethylbenzene in food is limited, it is assumed that food does not contribute significantly to the daily intake of ethylbenzene.

TABLE IV-II

Estimated Intake of Ethylbenzene from the Environment by Adult Males in µg/kg/day

Concentration in drinking water (µg/ℓ)	Estimated Total Intake in µg/kg/day (percent from drinking water) Based on Air Levels of:		
	Rural/remote (2.0 µg/m³)	Urban/suburban (5.2 µg/m³)	Maximum (14,000 µg/m³)
0.0	0.66 (0%)	1.7 (0%)	4,600 (0%)
0.5	0.67 (2.1%)	1.7 (0.8%)	4,600 (0.0003%)
5.0	0.8 (17.5%)	1.8 (7.8%)	4,600 (0.003%)

Intake from each source:

Water:	0.5 µg/ℓ:	0.014 µg/kg/day
	5.0 µg/ℓ:	0.14 µg/kg/day
	10.0 µg/ℓ:	0.29 µg/kg/day
Air:	2.0 µg/m³:	0.66 µg/kg/day
	5.2 µg/m³:	1.7 µg/kg/day
	14,000 µg/m³:	4600 µg/kg/day

Food: 0 µg/kg/day

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of ethylbenzene of 5.2 μg/m³ based on air monitoring data. Assuming an air level of 5.2 μg/m³ and the estimated ethylbenzene intake of 0 μg/kg/day from foods, drinking water would be the predominant source of ethylbenzene exposure in the adult male only at drinking water levels >60 μg/ℓ. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of ethylbenzene in drinking water and low concentrations of ethylbenzene in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for ethylbenzene by route of exposure. In addition, the effects of the chemical on the body may vary by different routes of exposure.

References

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Prepared by SRI International, Menlo Park, CA for Environ. Sci. Res. Lab., ORD, U.S. EPA, Triangle Park, NC. Contract No. 68-02-3452.

Close, J., K. Slade and K. Maskussen. 1982. Report of 1981 organic chemical surveillance survey at community water systems in New York State. New York State Dept. Health, Bureau of Public Water Supply Protection.

ICRP (International Commission on Radiological Protection). 1975. Report of the task group on reference man. ICRP Publ. 23. Pergamon Press, New York.

Kinlin, T.E., R. Muralidhara, A.O. Pittet, A. Sanderson and J.P. Walradt. 1972. Volatile components of roasted filberts. Agric. Food Chem. 20(5): 1021-1028.

Oldham, R.G., R.L. Spraggins, J.L. Parr and K.W. Lee. 1979. Analysis of organics in ambient air. Radian Corporation, Austin, TX. (Cited in Brodzinsky and Singh 1982)

Shackelford, W.M., D.M. Cline, L. Burchfield, L. Faas, G. Kurth and A.D. Sauter. 1981. Computer survey of gas chromatography/mass spectrometry data acquired in the U.S. Environmental Protection Agency screening analysis: system and results. Chapter 33. In: Advances in the Identification and Analysis of Organic Pollutants in Water, Vol. 2., L.H. Keith, Ed. Ann Arbor Science Publishers, Inc., Ann Arbor, MI. p. 527-554.

Shackelford, W.M. and L.H. Keith. 1976. Frequency of organic compounds identified in water. Environ. Res. Lab., ORD, U.S. EPA, Athens, GA. EPA 600/4-76-062.

U.S. EPA. 1975a. Analytical Report: New Orleans area water supply study. U.S. EPA, Region VI, Dallas, TX. EPA 906/9-75-003.

U.S. EPA. 1975b. Preliminary assessment of suspected carcinogens in drinking water. OTS, U.S. EPA, Washington, DC.

U.S. EPA. 1983. Groundwater Supply Survey. Computer data file provided by ODW, Technical Support Division, U.S. EPA, Cincinnati, OH.

V. HEALTH EFFECTS IN ANIMALS

General Toxicity

Acute Toxicity. The acute toxicity of ethylbenzene, administered as a single oral dose (in olive or corn oil solution) by stomach tube, was determined in Wistar-derived rats of both sexes (Wolf et al., 1956). Surviving rats were observed for ~2 weeks to assure recovery. The reported LD_{50} determined for 57 rats of both sexes was 3.5 g/kg bw. Similarly, Smyth et al. (1962) reported that the acute oral LD_{50} in fasted male Carworth-Wistar rats, determined after a 14-day observation period, was 5.46 g ethylbenzene/kg bw. Seven of 10 fasted rats (strain not specified) treated with 2.5 mℓ of a 1:1 olive oil mixture (1.1 g ethylbenzene/rat or ~4.4 g/kg) by gavage died within 21 days of treatment (Gerarde, 1959). Deaths were due primarily to pulmonary failure from hemorrhage and congestion of pulmonary capillaries and alveoli. A single oral dose of 6.0 g/kg was reported to cause death in all treated rats and mice, but neither the strains nor numbers of animals in the treated groups were specified (Faustov, 1958). The length of the observation period was not stated.

Following acute exposure to concentrated ethylbenzene vapors, the maximum time for exposure causing no deaths in male Carworth-Wistar rats was 1 hour. At 8000 ppm (~34,780 mg/m³) all rats (6/6) exposed for 4 hours died. Four hours of inhalation exposure at 4000 ppm (~17,400 mg/m³) was lethal to 3 of 6 rats (Smyth et al., 1962). Faustov (1958, 1960) reported that the concentration of ethylbenzene causing death in all animals after a 2-hour inhalation exposure was 50 mg/ℓ (50,000 mg/m³) for mice and 70 mg/ℓ (70,000 mg/m³) for rats (strains and numbers not specified). The

LC_{50} in mice after a similar exposure was 35.5 mg/ℓ (35,500 mg/m³). The LC_{50} for ethylbenzene vapor was 58.04 mg/ℓ and that causing death in all animals was 70-75 mg/ℓ (58,040 and 70,000-75,000 mg/m³, respectively) in albino rats exposed for 2 hours (Ivanov, 1962a).

The acute dermal LD_{50} of ethylbenzene, applied to the clipped skin on the trunk of albino New Zealand rabbits and covered by plastic film, was 17.8 mℓ/kg (~15,400 mg/kg) (Smyth et al., 1962).

Exposure to ethylbenzene at 2000 ppm (8685 mg/m³) for 6 hours/day for 3 days resulted in significantly ($p<0.05$) increased liver to bw ratio and hepatic microsomal cytochrome P-450 content (190% of controls) in treated male Sprague-Dawley rats (Toftgard and Nilsen, 1981, 1982). Enzyme induction (increased activity) was reported to be significant ($p<0.05$) for NADPH cytochrome C reductase and 7-ethoxyresorufin deethylase (433% of controls). Hydroxylation of hexane (184, 1110 and 1270% increase above controls for 1, 2 and 3-hexanol, respectively) and benzo(alpha)pyrene metabolism to its 4,5-diol (1060% of controls) also were increased in liver microsomal preparations from ethylbenzene-treated rats when compared with controls ($p<0.05$) (Toftgard and Nilsen, 1981). The kidney weight was also elevated significantly , as was renal NADPH-cytochrome C reductase activity in treated rats ($p<0.05$) (Toftgard and Nilsen, 1982). Microsomal preparations from the lungs of ethylbenzene-treated rats were slightly less active in forming hexanol from hexane and o-deethylation of 7-ethoxyresorufin. The effects observed, however, were significantly different from control ($p<0.05$).

Exposure to ethylbenzene by inhalation at 2000 ppm (8696 mg/m³) for 6 hours/day on 3 consecutive days did not cause a significant change in dopamine or catecholamine levels in the hypothalamus or median eminence of exposed male Sprague-Dawley rats (Andersson et al., 1981). The rate of turnover of dopamine and catecholamines, determined by the injection of a tyrosine hydroxylase inhibitor and subsequent fluorimetric measurement of dopamine and catecholamine depletion, was increased significantly in several regions of the forebrain and hypothalamus. These investigators also reported that serum prolactin levels in the exposed rats were 30% lower than the serum prolactin levels in the control group rats.

The effects of acute exposure to ethylbenzene in the LD_{50} experiment included slight liver and kidney changes of questionable significance (incidence not specified) in some rats (Wolf et al., 1956). Inhalation exposure at 0.78 mg ethylbenzene vapor/ℓ (780 mg/m³) was reported as the threshold level causing observable effects on the central nervous sytem in mice (Faustov, 1958). Ethylbenzene vapors at 15 mg/ℓ (15,000 mg/m³) for 2 hours caused mice to "fall on their sides" (Faustov, 1958). In an English abstract of a Russian study, Ivanov (1962a) reported that ethylbenzene inhalation over 2 hours caused loss of coordination, narcosis, convulsions and irritation to the respiratory mucosa and eyes in treated rats. Inhalation of ethylbenzene at 410-9640 ppm (1783-41,913 mg/m³) for 30 minutes by mice caused pulmonary irritation and nervous system depression, which caused an anesthetic effect in a dose-related fashion (Nielsen and Alarie, 1982). Mice exposed at concentrations >7800 ppm were sedated. The concentration

given for 30 minutes that caused a 50% decrease in respiratory rate (RD_{50}) for ethylbenzene in mice was 4060 ppm (17,650 mg/m³) (Nielsen and Alarie, 1982).

Concentrated ethylbenzene applied to the eyes of rabbits (two drops applied) caused perceptible irritation of the conjunctiva but no apparent corneal damage (Wolf et al., 1956). Smyth et al. (1962) reported that there was only slight necrosis of the cornea and some irritation to the shaved abdomens of rabbits after undiluted ethylbenzene was applied.

Subchronic and Chronic Exposure. The toxicity of ethylbenzene, administered in olive oil by stomach tube 5 days/week for 6 months, was tested on groups of 10 female Wistar rats (Wolf et al., 1956). Test groups received 13.6, 136, 408, 680 mg ethylbenzene/kg bw/day or olive oil (2.5 ml) only (vehicle control) for 130 days of the 182-day experiment. No effects were noted in groups of rats exposed at 13.6 and 136 mg/kg/day. At the two higher dose levels, increases in liver and kidney weights were reported. There were also slight histopathological changes of the liver and kidney, including cloudy swelling of hepatocytes and renal tubular epithelium (Wolf et al., 1956). Pokkrovskii and Volchkova (1968) reported that 400 mg ethylbenzene/kg bw administered (presumably orally on a daily basis) to rabbits for 6 months caused segmentation of nuclei of all leukocytic blood cells. The significance, if any, of this effect on the health of rabbits was not discussed.

The effects of repeated exposure to ethylbenzene by vapor inhalation have been examined in rats, guinea pigs, rabbits and rhesus monkeys (Wolf et

al., 1956). Ten to 25 rats, 5-10 guinea pigs, 1-2 rabbits and 1-2 monkeys of either sex were exposed at each dose level. Rats of both sexes were exposed at 400, 600 or 1250 ppm (1700, 2600 or 5400 mg/m^3) and males were exposed at 2200 ppm (9500 mg/m^3). The exposure duration was 7 hours/day on 4-5 days/week for 144-214 days. There were 103 to 138 exposures during the study. Liver and kidney weights were increased slightly in all exposed groups compared with matched controls, and rats treated at 1250 and 2200 ppm ethylbenzene developed cloudy swelling of the liver and renal tubules. Growth was depressed moderately in male rats treated at 2200 ppm. In guinea pigs and rabbits, animals of both sexes were exposed to 400 or 600 ppm (1700 or 2600 mg/m^3), 7 hours/day, 5 days/week over a 186-day period. Additionally, female guinea pigs and rabbits were exposed to 1250 ppm (5400 mg/m^3) for 7 hours/day, 138 times over 214 days. In guinea pigs, growth was depressed in females treated at 1250 ppm, liver weight was increased in the group treated at 600 ppm, and no effects were evident in the lowest dose group. The only effect reported in rabbits was a slight degeneration of the testicular germinal epithelium in males treated at 600 ppm ethylbenzene. Rhesus monkeys treated at 600 ppm for 7 hours/day, 5 days/week for 186 days had increased liver weights and males had slight testicular degeneration. No effect was reported in the female rhesus monkeys treated at 400 ppm over the same period (Wolf et al., 1956).

In the following Russian studies, available only as English abstracts, effects were reported at ethylbenzene levels lower than most of the studies discussed above. Details of the Russian studies and the extent or signifi-

cance of the effects were not specified, except as indicated below. Exposure to ethylbenzene vapors at 0.1 and 1.0 mg/ℓ (100 and 1000 mg/m³) for 4 hours/day (number of days/week not specified) during 7 months caused leukocytosis with an increase in nuclear-segmented neutrophils, a decrease in lymphocytes, an increase in reticulocytes, decreased serum albumins and increased serum globulin proteins (Ivanov, 1962b). Later, Ivanov (1964) reported that exposure at 1.0 mg/ℓ caused lipid dystrophia in the liver, renal dystrophy, muscle chronaxia and altered blood cholinesterase activity. Faustov and Kramsakov (1968) reported that the titer of antibodies (type not specified) and the bactericidal properties of the blood were decreased in rabbits chronically exposed to 1.5 mg ethylbenzene/ℓ (1500 mg/m³) and immunized with dysentery vaccine.

Ethylbenzene applied to the ears and shaved abdomens of rabbits for 2-4 weeks (10-20 applications) caused moderate irritation with erythema and moderate necrosis, and desquamation with some cutaneous blistering (Wolf et al., 1956).

No chronic exposure studies were found in the available literature.

Target Organ Toxicity

The data presented in the Acute Toxicity and Subchronic and Chronic Exposure Sections concerning target organ toxicity are summarized in Table V-1. These data indicate that the liver, kidney and central nervous system are the principal target organs of ethylbenzene. Subchronic exposure at levels ~400 mg/kg/day (oral) or 1250 ppm (inhalation) caused increases in liver and kidney weights as well as slight cytopathologies (Wolf et al.,

TABLE V-1

Target Organ Toxicity of Ethylbenzene

Route of Administration	Species/Strain	Sex	Number	Dose	Duration	Vehicle	Organ	Effect	Reference
Oral	rat/Wistar	M,F	57	3.5 g/kg	single dose	olive or corn oil	liver	Slight histolological change[a]	Wolf et al., 1956
							kidney	Slight histological change[a]	
Oral	rat/NS	NS	10	3.2 g/kg[b]	single dose	olive oil	lung	Pulmonary failure; congestion, hemorrhage	Gerarde, 1959
Oral	rat/Wistar	F	10	13.6 or 136.0 mg/kg/day x 5 days/week	182 days	olive oil	NS	No effect noted on liver or kidney	Wolf et al., 1956
Oral	rat/Wistar	F	10	408 or 680 mg/kg/day x 5 days/week	182 days	olive oil	liver	Increased relative weight; cloudy swelling of tubular epithelium.	Wolf et al., 1956
							kidney	Increased relative weight; cloudy swelling of tubular epithelium.	
Inhalation	mice/Swiss-Webster	M	4	410-9640 ppm	30 minutes	air	CNS	Dose-related progression of depression anesthesia and loss of coordination.	Nielsen and Alarie, 1982
							lung	Irritation, decreased respiratory rate.	
Inhalation	rat/Sprague-Dawley	M	6	2000 ppm x 6 hours/day	3 days	air	brain	No effect on dopamine or catecholamine levels.	Andersson et al., 1981
							serum	70% reduction in prolactin levels.	

TABLE V-1 (cont.)

Route of Administration	Species/Strain	Sex	Number	Dose	Duration	Vehicle	Organ	Effect	Reference
Inhalation	rat/Sprague-Dawley	M	4	2000 ppm x 6 hours/day	3 days	air	liver	Increased relative weight; increased P-450 and NADPH-cytochrome C reductase.	Toftgard and Nielsen, 1981, 1982
							kidney	Increased relative weight; increased NADPH-cytochrome C reductase.	
Inhalation	rat/Wistar	M,F	10-25[c]	400 or 600 ppm x 7 hours/day	186 days	air	liver and kidney	Slight increase in relative weight.	Wolf et al., 1956
Inhalation	rat/Wistar,	M,F	10-25[c]	1250 or 2200 ppm[d] x 7 hours/day	214 or 144 days	air	liver	Increased relative weight; slight cloudy swelling of hepatocytes.	Wolf et al., 1956
							kidney	Increased relative weight; slight cloudy swelling of tubular epithelium.	
Inhalation	guinea pig/albino	M,F	5-10[c]	600 ppm x 7 hours/day	186 days	air	liver	Slight increased relative weight.	Wolf et al., 1956
Inhalation	rabbit/albino	M,F	1-2[c]	600 ppm x 7 hours/day	186 days	air	testes	Degenerative germinal epithelium.	Wolf et al., 1956
Inhalation	monkey/Rhesus	M,F	1-2[c]	600 ppm x 7 hours/day	186 days	air	liver	Slightly increased relative weight.	Wolf et al., 1956
							testes	Degenerative germinal epithelium	

[a]Included slight cloudy swelling of hepatocytes and tubular epithelium in some animals.

[b]Assuming a 0.35 kg rat

[c]A variable number of animals were used at each ethylbenzene level.

[d]Only male rats were exposed at 2200 ppm ethylbenzene for 144 days.

NS= Not Specified

1956). Lower inhalation doses (400 and 600 ppm) affected liver and kidney weights; however, no histopathology was observed. Anesthetic effect and loss of coordination were apparent after acute inhalation exposure at levels >7800 ppm (Nielsen and Alarie, 1982). One study also indicated testicular degeneration in rabbits and rhesus monkeys subchronically exposed to ethylbenzene at 600 ppm by inhalation for 7 hours/day for 5 days/week (Wolf et al., 1956).

Other Effects

Carcinogenicity. Pertinent data regarding the carcinogenicity of ethylbenzene could not be located in the available literature. Ethylbenzene has been selected by the National Cancer Institute and assigned to the bioassay program for carcinogenicity testing (NCI, 1983). These bioassays usually expose rats (F344) and mice (B6C3F1) of both sexes to the chemical for a period of 2 years. Preliminary testing (range-finding studies) has not been initiated.

Mutagenicity. The mutagenic activity of ethylbenzene was tested in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 with and without a rat liver activation system (Florin et al., 1980). Rats were pretreated with 3-methylcholanthrene or Aroclor before preparation of the liver homogenate. No mutagenic activity was evident in plate incorporation assays when 0.03, 0.3, 3.0 and 30.0 µmol/plate (0.003, 0.032, 0.319 and 3.185 mg/plate) were tested on any of the tester strains with or without the microsomal activation. At 30 µmol/plate ethylbenzene was toxic to the bacteria (absence of bacterial lawn). Ethylbenzene was not mutagenic when tested at 0.4 mg/plate in the plate incorporation assay in the presence of

an Aroclor 1254-induced rat liver microsomal preparation on S. typhimurium strains TA1535, TA100, TA1537, TA1538 and TA98 (Nestmann et al., 1980). In the Drosophila recessive lethal test, pure ethylbenzene did not increase the frequency of recessive lethals. Technical xylene, however, containing 18.3% ethylbenzene, caused a slight increase in recessive lethals (Donner et al., 1979).

Teratogenicity. Inhalation experiments were conducted with Wistar or Sprague-Dawley rats (not differentiated in report) and New Zealand white rabbits exposed during days 1-19 and 1-24 of gestation, respectively (Hardin et al., 1981). An additional group of rats was exposed to ethylbenzene for 3 weeks before mating and during gestation. Both species were exposed for 6-7 hours/day at 100 or 1000 ppm (435 or 4348 mg/m^3). All pregnant animals were sacrificed 1 day before term (21 days for rats; 30 days for rabbits). Maternal organs (liver, lungs, kidney, heart, spleen, adrenals, ovaries and brain) were examined grossly, weighed and examined histopathologically. Uteri were examined and fetuses weighed, sexed, measured for crown-rump length and examined for external, internal and skeletal abnormalities. Rabbits exposed at both levels of ethylbenzene vapor had a significantly ($p<0.05$) reduced number of live kits/litter, but dead or resorbed fetuses were not increased above matched controls. Terata among exposed embryos were not increased. Maternal toxicity in the rabbits was not evident. Female rats, however, exposed at 1000 ppm had increased liver, kidney and spleen weights indicating maternal toxicity. In rats exposed before breeding at both levels of ethylbenzene (combined), 77% of the sperm-positive females became pregnant, while in matched controls, 89% of the sperm-positive females became pregnant. Because a dose-related effect on

fertility was not evident, this was not reported as a clear reduction in fertility. There was a significant ($p<0.05$) increase in the incidence of extra ribs in both groups exposed at 1000 ppm (before and during gestation) and those exposed at 100 ppm during gestation, but this was regarded by the authors as only suggestive rather than indicative of teratogenic potential. Fetal toxicity in the rats was not evident.

Marks et al. (1982) reported that a xylene mixture containing 17.0% ethylbenzene was teratogenic to mice when administered at 2.1, 2.6 or 3.1 g/kg/day ($p<0.01$) when compared with vehicle controls. One-third the daily dose was administered 3 times/day by gavage on days 6-15 of gestation. All dams died at the highest dose of 4.1 g/kg/day. Twelve of 38 dams treated at 3.1 g/kg/day died on day 18. No statistically significant increases in malformations were observed at the two lowest doses (0.6 and 1.2 g/kg/day), although a significant trend was associated with increasing dosage. Cleft palate was the major terata, with increased wavy ribs in exposed groups. Because of the mixed exposure it was not possible to ascertain whether ethylbenzene was instrumental in causing the abnormalities.

Summary

The acute toxicity of ethylbenzene is apparently quite low with an oral LD_{50} value of 3.5 g/kg in rats (Wolf et al., 1956). Inhalation of 4000 ppm (1737 mg/m^3) ethylbenzene for 4 hours was lethal to 3 of 6 exposed rats (Smyth et al., 1962). Subchronic oral exposure to levels as high as 136 mg/kg/day resulted in no observable adverse effects in rats (Wolf et al., 1956). Slight toxic effects were evident in rats exposed at 400 ppm by inhalation (7 hours/day, 5 days/week) for a period of 6 months (Wolf et al.,

1956). In rabbits, guinea pigs and female rhesus monkeys exposed to 400 ppm (1737 mg/m³) ethylbenzene for a similar period, no effects were evident. Toxic effects are evident predominantly in the liver and kidney by inhalation or ingestion, with an anesthetic effect on the nervous system when exposure is by inhalation. Several Russian studies have reported cellular and biochemical effects after exposure to ethylbenzene at levels as low as 0.1 mg/ℓ (23 ppm). These studies, however, lack details necessary for their evaluation and do not note whether effects would affect the health of exposed animals. Ethylbenzene has not been tested adequately for carcinogenicity. In the mutagenicity tests conducted, ethylbenzene has not been shown to be a mutagen. Based on the limited studies conducted using rats and rabbits, the potential teratogenicty of ethylbenzene cannot be assessed adequately.

VI. HEALTH EFFECTS IN HUMANS

Clinical Case Studies

After exposing 18 human male volunteers to 100 ppm (434 mg/m³) ethylbenzene for 8 hours, Bardodej and Bardodejova (1970) reported that no damage to health was evident. If exposure exceeded this level, however, subjects reported symptoms such as sleepiness, fatigue, headache and mild eye and respiratory irritation. The authors did not state the actual amount of increase. Volunteers were presumably at rest during the exposure. Gamberale et al. (1978) reported that volunteers exposed to a mixture of xylene containing 20.7% ethylbenzene showed a decrease in performance during flicker fusion (the frequency of stroboscopic light pulses that the subject sees as continuous illumination), reaction time and short-term memory tests when exposure to the mixture was 1300 mg/m³ (269 mg/m³ ethylbenzene) during a 70-minute exposure period.

The threshold values for taste and odor detection by humans were reported to be 0.1 and 0.2 mg ethylbenzene/ℓ water, respectively (Faustov, 1958). The odor threshold in air was reported as 0.002-0.0026 mg/ℓ (0.6 ppm) (Ivanov, 1962a). These Russian reports were available only as English abstracts and details of the studies are lacking. Gerarde (1959) reported that ethylbenzene at 200 ppm was the threshold for irritation of the mucous membranes and conjunctiva.

Epidemiological Studies

The TLV for ethylbenzene is 100 ppm (435 mg/m³) (ACGIH, 1980). This level is defined as the time-weighted average for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly

exposed, day after day, without adverse effects (ACGIH, 1981). It is not a NOAEL for systemic toxicity since this value was established to prevent irritation.

Mihail et al. (1972) reported that workers exposed to chemicals including ethylbenzene (levels not reported) for ≥5 years in the rubber industry had elevated serum ornithine carbamoyltransferase activity. Vinokurova (1970) noted that workers in the rubber industry who had been exposed to unspecified levels of ethylbenzene, styrene and butadiene for 8 years had dystrophic changes of the myocardium, which affected heart contractility. Details of the Russian study concerning the number of workers, controls or procedures used to detect changes in the heart were not available in the English abstract.

High Risk Subpopulations

Workers exposed to technical grade xylene, which contains up to 20% ethylbenzene, and chemical plant workers dealing with pure ethylbenzene (styrene synthesis) would be at the highest risk of ethylbenzene intoxication (ACGIH, 1980). Ethylbenzene is manufactured predominantly for the production of styrene; consequently, workers producing ethylbenzene or styrene would represent the largest high-risk subpopulation.

Ethylbenzene has been detected in maternal and fetal cord blood, indicating placental transfer (Dowty et al., 1976). Fetal accumulation or toxicity was not discussed.

Summary

Data regarding the effects of ethylbenzene on humans are limited. Acute, 8-hour exposures at levels >100 ppm have reportedly caused fatigue, headache and mucous membrane irritation (Bardodej and Bardodejova, 1970). The TLV based on irritation prevention is 100 ppm (435 mg/m³). The irritation threshold is 200 ppm (870 mg/m³) in the air (Gerarde, 1959). Odor and taste thresholds in water are 0.2 and 0.1 mg/ℓ, respectively, while odor detection from air is near 0.002 mg/ℓ (2 mg/m³). Data regarding occupationally-exposed humans indicate that ethylbenzene is encountered usually in mixtures with other chemicals (xylenes and styrene), and any described toxicity is attributed usually to the other, more toxic, constituents.

VII. MECHANISMS OF TOXICITY

There is only limited information about the possible mechanism of ethylbenzene toxicity. In an early study, Gerarde (1959) compared the nerve toxicity of a number of alkylbenzenes with their physical and chemical properties. The author noted in general that the compounds with highly lipophilicity and short side-chains were more effective in producing nervous system depression than alkylbenzenes which contain polar constituents or have bulky side-chains. Gerarde (1959) proposed that small nonpolar alkylbenzenes, such as ethylbenzene, would penetrate rapidly into nerve cells and disrupt nerve function by a nonspecific mechanism similar to the way in which a solute changes the properties of a solvent. He also noted that hemorrhage in the lungs occurred after administration of large doses of ethylbenzene regardless of the route of administration. These results were attributed to nonspecific disruption of the permeability properties of the endothelial cell membranes after accumulation of nonpolar ethylbenzene in the lipophilic cell membrane.

Although the actual mechanism of ethylbenzene toxicity may be more complex than that proposed by Gerarde (1959), a more recent in vitro study using erythrocytes suggests that ethylbenzene and other anesthetic compounds can affect membrane function in a nonspecific manner (Holmberg et al., 1974). In this study, the rate of hemolysis of rat erythrocytes in hypotonic saline was compared when different organic solvents were added to the incubation media. When cells were incubated with 48 ppm (mg/ℓ) of ethylbenzene, maximum protection from hemolysis was obtained. This protection from hemolysis required the presence of ethylbenzene in the media since washed erythrocytes preincubated with ethylbenzene had the same rate of hemolysis as untreated cells.

In the study by Holmberg et al. (1974), there was a correlation between the antihemolytic properties of the organic compounds tested and their isooctanol/water partition coefficient. The more hydrophobic compounds provided greater protection from hemolysis. The authors suggested that these anesthetic compounds partitioned into the cell membrane in proportion to their lipophilicity and that resulting changes in the organization of the membrane were, at least in part, responsible for the antihemolytic effect. It was noted that protection from hemolysis occurred at compound levels which anesthetized nerve fibers and that higher concentrations resulted in destabilization of the membrane and greater sensitivity to the hemolytic action of hypotonic saline.

Synergistic and Antagonistic Interactions

The excretion of thiocyanate (a metabolite of acrylonitrile) after simultaneous exposure to acrylonitrile (0.5 mmole/kg, orally) and ethylbenzene (0.5 mmole/kg, subcutaneously) was reduced by nearly 50% in male Wistar rats compared with acrylonitrile-only treated animals (Gut et al., 1981). In female Velaz albino mice, mortality among acrylonitrile-only treated animals (1.13 mmole/kg, intraperitoneally) was 0/24, while in those treated with the same dose of acrylonitrile and ethylbenzene (3.39 mmole/kg, subcutaneously, 2 hours before acrylonitrile), 14/16 died within 2 days. These data show a significant ($p<0.05$) potentiation effect of acrylonitrile toxicity by ethylbenzene (Gut et al., 1981). In a similarly conducted study, Elovaara et al. (1982) reported that m-xylene metabolism was preferred over ethylbenzene metabolism when both were administered to male Wistar rats for 5 days (6 hours/day; 600 and 200 ppm, respectively). This pattern, if present in humans, may be important since workers are often exposed to

xylene and ethylbenzene as a mixture (technical grade xylene as a solvent contains ~20% ethylbenzene) (Andersson et al., 1981).

Summary

Several different mechanisms of action have been postulated for ethylbenzene based on acute and chronic toxic effects. Because of its affinity for lipid-containing tissues, ethylbenzene may accumulate in nervous tissue, causing oxygen deprivation and altered metabolism, leading to nervous depression and narcosis. Ethylbenzene also stresses both the liver and kidney which are sites of metabolism and elimination. Pulmonary damage including congestion and hemorrhage caused by the irritant effect of ethylbenzene on epithelia may be the ultimate cause of mortality after acute exposure even in animals treated by noninhalation routes (Gerarde, 1959).

Ethylbenzene has been shown to potentiate the toxicity of acrylonitrile dramatically in rats and mice after acute exposures (Gut et al., 1981). When ethylbenzene and m-xylene are administered simultaneously, m-xylene is preferentially metabolized, causing ethylbenzene metabolism to be delayed (Elovaara et al., 1982).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level
LOAEL = lowest-observed-adverse-effect level
Body weight = 70 kg for adult or 10 kg for child
Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children
Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited

period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identifying a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC, 1977) for selection of an uncertainty factor, but must be considered,

include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen, mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. There is insufficient evidence to classify ethylbenzene as a carcinogen following oral exposure The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and

random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Existing Standards and Criteria

The occupational standard (TWA) in air and the TLV have been set at 100 ppm (435 mg/m^3) (ACGIH, 1980). This level is set to protect against irritation of the mucous membranes and other symptoms such as headache and fatigue.

Using calculations based upon the TLV of 100 ppm, the U.S. EPA (1980) developed an ambient water quality criterion of 1.4 mg/ℓ which assumed consumption of 2 ℓ of water and 6.5 g of contaminated fish/seafood/day and a bioconcentration factor of 37.5. The protected individual was a 70 kg adult exposed for a 70 year lifetime. Drinking water contributed 89% of the exposure; the fish/seafood contributed the remaining 11%.

Noncarcinogenic Effects

The oral LD_{50} determined in tests with 57 rats of both sexes treated by gavage was 3.5 g/kg bw (Wolf et al., 1956). Supporting this value, Gerarde (1959) reported that 7 of 10 rats treated with ~1.1 g of ethylbenzene by gavage (~4.4 g/kg in a 250 g rat) died as a result of treatment. During a 6-month oral testing of ethylbenzene in rats, Wolf et al. (1956) reported that no effects were evident at 13.6 and 136.0 mg/kg/day. Effects were reported, however, at 408 and 680 mg/kg/day. Exposure at 400 ppm ethylbenzene vapor (1700 mg/m^3) in rats may be assumed to be a LOEL, since only slight increases in liver and kidney weights were reported (Wolf et al., 1956). In rabbits, guinea pigs and rhesus monkeys, no observable effects were reported following a 6-month exposure at 400 ppm ethylbenzene (1700 mg/m^3). A LOEL for the three species was 600 ppm (2600 mg/m^3) (Wolf et al., 1956).

In humans, 100 ppm (435 mg/m^3) ethylbenzene for 8 hours caused no signs of toxicity (Bardodej and Bardodejova, 1970). This is assumed to be a NOAEL for irritation, but does not necessarily establish a NOAEL for target organ toxicity. Unspecified levels >100 ppm became irritating to mucous membranes and caused headache and fatigue.

The absorption coefficient of ethylbenzene vapor following inhalation exposure is assumed to be 0.5 for purposes of dose calculation. This factor is substantiated by indirect estimates of ethylbenzene vapor absorption in rats and humans. Chin et al. (1980a) concluded that over a 6-hour period, rats exposed at 1000 mg/m^3 would inhale 36 mg of ethylbenzene. Data showed, however, that ~16 mg of ethylbenzene/rat was required to maintain

the chamber concentration. Hence, they concluded that this 16 mg ethylbenzene/rat was absorbed and the absorption coefficient was 44% (16 mg absorbed ÷ 36 mg inhaled). Bardodej and Bardodejova (1970) reported that in humans, 64% of the inhaled ethylbenzene (8-hour exposure at various concentrations) was retained in the respiratory tract. The procedural details of this determination were not explicated. These data suggest that 0.5 is a reasonable estimate of ethylbenzene absorption following inhalation.

Quantification of Noncarcinogenic Effects

1-Day HA. The derivation of a 1-day HA for ethylbenzene can be based on the 100 ppm (435 mg/m³) NOAEL for ethylbenzene in humans exposed for 8 hours (Bardodej and Bardodejova, 1970). Assuming an inhalation absorption efficiency of 50%, based on human and rat data (Chin et al., 1980a; Bardodej and Bardodejova, 1970), the daily transformed dose (d) and the 1-day HA would be derived as follows:

Transformed dose

$$d = 435\ mg/m^3 \times 20\ m^3/day \times 8/24 \times 0.5 \div 70\ kg$$
$$= 20.7\ mg/kg/day$$

1-day HA for an adult

$$HA = (20.7\ mg/kg/day \times 70\ kg) \div (10 \times 2\ \ell/day)$$
$$\sim 73\ mg/\ell$$

1-day HA for a child

$$HA = (20.7\ mg/kg/day \times 10\ kg) \div (10 \times 1\ \ell)/day$$
$$\sim 21\ mg/\ell$$

Where

435 mg/m³	= a NOAEL for human inhalation exposure
20 m³	= assumed volume of air inhaled in 24 hours
8/24	= conversion of 8 hours/day exposure to continuous 24 hours/day exposure
0.5	= assumed absorption efficiency
70 kg	= weight of protected individual if an adult
10 kg	= weight of protected individual if a child
2 ℓ	= volume of water imbibed/day by a 70 kg adult (2 ℓ)
1 ℓ	= volume of water imbibed/day by a 10 kg child (1 ℓ)
10	= uncertainty factor appropriate for use with human data

10-Day HA. Because of the lack of appropriate exposure duration data, the 10-day HA will be derived from the 1-day HA. The 1-day HA will be divided by 10 to give estimated 10-day HA values. The resulting 10-day HA for a child would be as follows:

$$\text{10-Day HA} = \frac{21\ \text{mg/ℓ}}{10} = 2.1\ \text{mg/ℓ}$$

for an adult:

$$\text{10-Day HA} = \frac{73\ \text{mg/ℓ}}{10} = 7.3\ \text{mg/ℓ}$$

Lifetime AADI. The most appropriate data for the derivation of an AADI are those from rats treated orally at four dose levels of ethylbenzene 5 days/week for 6 months (Wolf et al., 1956). No observable effects were reported in groups exposed at 13.6 and 136 mg/kg/day, while histopathological changes were evident in groups treated at 408 and 680 mg/kg/day. If, then, it were assumed that the highest NOEL in this study was 136 mg/kg/day, and, that all of this dose was absorbed, an AADI for a 70 kg adult would be derived as follows:

$$\text{AADI} = \frac{136\ \text{mg/kg/day} \times 100\% \times 5/7 \times 70\ \text{kg}}{100 \times 10 \times 2\ \text{ℓ/day}} = 3.4\ \text{mg/ℓ}$$

Where

136 mg/kg/day = subchronic oral NOEL from animal study

100% = assumed percentage of absorption

5/7 = conversion of 5 days/week dosing regimen to continuous 7 days/week exposure pattern

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use with animal NOEL data, with no comparable human data

10 = uncertainty factor, appropriate for use with data from exposure duration significantly less than lifetime

2 ℓ = volume of drinking water imbibed/day by 70 kg adult

Carcinogenic Effects

Pertinent data regarding the possible carcinogenicity of ethylbenzene could not be located in the available literature. A long-term carcinogenicity bioassay has been initiated but data are not available (NCI, 1983). Given the available mutagenicity testing in Salmonella typhimurium strains, ethylbenzene does not appear to be a mutagen (Florin et al., 1980; Nestmann et al., 1980).

Quantification of Carcinogenic Effects

Because of the lack of data, an assessment of the carcinogenic risk of ethylbenzene is not possible at this time.

Special Considerations

Synergistic Effects. Ethylbenzene has been shown to potentiate the toxicity of acrylonitrile in treated mice. Mortality was 0/24 in mice given single intraperitoneal injections of acrylonitrile alone (1.13 mmole/kg),

while 14/16 died when pretreated with ethylbenzene (subcutaneously to 3.39 mmole/kg) (Gut et al., 1981). Simultaneous exposure to acrylonitrile and ethylbenzene in rats resulted in delayed metabolism of thiocyanate (acrylonitrile metabolite).

In rats exposed to ethylbenzene and m-xylene simultaneously, m-xylene metabolism was preferred and ethylbenzene metabolism was delayed (Elovaara et al., 1982). The effects of delayed ethylbenzene metabolism on accumulation, metabolism and toxicity were not determined. The interaction between m-xylene and ethylbenzene may be significant, since workers are often exposed to technical xylene solvent, which contains up to 20% ethylbenzene.

High Risk Subpopulations. As noted in Chapter VI, workers exposed to technical grade xylene solvent and those involved in the synthesis of ethylbenzene and the production of xylene may be at a higher risk of ethylbenzene bioaccumulation and toxic effects. Ethylbenzene has also been shown to increase the toxicity of acrylonitrile by inhibiting its metabolism. Therefore, workers exposed to acrylonitrile, and possibly other chemicals, may be at a higher risk of other intoxication because of ethylbenzene exposure.

Although ethylbenzene was not shown to be teratogenic or fetotoxic in rats or rabbits (Hardin et al., 1981), it has been detected in cord blood of humans, indicating its transplacental transfer. Fetuses may be more susceptible to ethylbenzene because of lower levels of hepatic metabolism, but confirming data are not available.

Summary

The values for the quantification of toxicological effects of ethylbenzene are summarized in Table VIII-1. The 1-day HAs for noncarcinogenic effects in a 10 kg child and 70 kg adult are derived from the NOAEL in humans (Bardodej and Bardodejova, 1970). The values are 21 and 73 mg/ℓ for the child and adult, respectively. The 10-day HA for a child and adult are derived from the 1-day HA because of the lack of appropriate toxicity data. These values were 2.1 and 7.3 mg/ℓ, respectively. The lifetime AADI is determined using a conservative NOAEL value from a 6-month study in rats (Wolf et al., 1956). This value is 3.4 mg ethylbenzene/ℓ drinking water for a 70 kg adult consuming 2 ℓ water daily. The AADI assumes that the sole source of exposure to ethylbenzene is via the drinking water. [It is important to note that the taste and odor thresholds in water for ethylbenzene are 0.1 and 0.2 mg/ℓ, respectively (Fazzalari, 1978). Any maximum contaminant level (MCL) for ethylbenzene may have to consider the aesthetic, in addition to the toxic, consequences following exposure to ethylbenzene in drinking water.] Because of the lack of data, an assessment of the carcinogenic risk of ethylbenzene was not made.

No clear-cut high risk groups were identified, but workers exposed to ethylbenzene and acrylonitrile, m-xylene or possibly other chemicals may be affected at lower levels than people exposed to ethylbenzene alone.

TABLE VIII-1

Summary of Data Used to Derive HA and AADI

Criteria	Dose	Duration	Effect	Value of HA or AADI		Reference
				Adult	Child	
1-day HA	20.7 mg/kg/day (435 mg/m³ x 20 m³/day x 8 hours/24 hours x 0.5 ÷ 70 kg)	8 hours	Human NOAEL	73 mg/ℓ (2.1 mg/kg/day)	21 mg/ℓ	Bardodej and Bardodejova, 1970
10-day HA	20.7 mg/kg/day	8 hours	Human NOAEL	7.3 mg/ℓ* (0.21 mg/kg/day)	2.1 mg/ℓ*	Bordodej and Bardodejova, 1970
AADI	136 mg/kg/day	6 months	Rat NOAEL	3.4 mg/ℓ (0.014 mg/kg/day)	NA	Wolf et al., 1956

*Appropriate subchronic data were not available; these values are based on the 1-day HA.

NA = Not applicable

IX. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Ethylbenzene. Documentation of the Threshold Limit Values, 4th ed. p. 176.

ACGIH (American Conference of Governmental Industrial Hygienists). 1981. TLVs Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with intended changes for 1981. Cincinnati, OH. p. 3.

Andersson, K., K. Fuxe, O.G. Nilsen, R. Toftgaard, P. Eneroth and J.A. Gustafsson. 1981. Production of discrete changes in dopamine and noradrenaline levels and turnover in various parts of the rat brain following exposure to xylene, ortho-, meta- and para-xylene, and ethylbenzene. Toxicol. Appl. Pharmacol. 60(3): 535-548.

Angerer, J. and G. Lehnert. 1979. Occupational chronic exposure to organic solvents: VIII. Phenolic compounds: Metabolites of alkylbenzenes in man: Simultaneous exposure to ethylbenzene and xylenes. Int. Arch. Occup. Environ. Health. 43(2): 145-150.

Bakke, O.M. and R.R. Scheline. 1970. Hydroxylation of aromatic hydrocarbons in the rat. Toxicol. Appl. Pharmacol. 16: 691-700.

Bardodej, Z. and E. Bardodejova. 1970. Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. Am. Ind. Hyg. Assoc. J. 31(2): 206-209.

Burns, L.H., D.M. Cline and R.R. Lassiter. 1981. Exposure Analysis Modeling Systems (EXAMS). Prepared by Environmental Research Lab, ORD, U.S. EPA, Athens, GA.

Callahan, M.A., M.W. Slimak, N.W. Gabel et al. 1979. Water-Related Enviromental Fate of 129 Priority Pollutants. Vol. II. Office of Water Planning and Standards, Washington, DC. EPA 440/4-79-029b.

Chin, B.H., J.A. McKelvey, T.R. Tyler, L.J. Calisti, S.J. Kozbelt and L.J. Sullivan. 1980a. Absorption, distribution and excretion of ethylbenzene, ethylcyclohexane and methylethylbenzene isomers in rats. Bull. Environ. Contam. Toxicol. 24: 477-483.

Chin, B.H., J.A. McKelvey, L.J. Calisti, S.J. Kozbelt and L.J. Sullivan. 1980b. A comparison of *in vivo* and *in vitro* (tissue explant) techniques: Metabolic profile of ethylbenzene in the rat and the dog. Bull. Environ. Contam. Toxicol. 25(2): 241-245.

Donner, M., J. Maki-Paakkanen, N. Norppa, M. Sorsa and H. Vainio. 1979. Genetic toxicology of xylenes. Mutat. Res. 74(3): 171-172.

Dowty, B.J., J.L. Laseter and J. Storer. 1976. The transplacental migration and accumulation in blood of volatile organic constituents. Pediatr. Res. 10(7): 696-701.

Dutkiewicz, T. and H. Tyras. 1967. Study of the skin absorption of ethylbenzene in man. Br. J. Ind. Med. 24(4): 330-332.

El Masry, A.M., J.N. Smith and R.T. Williams. 1956. The metabolism of alkylbenzenes: n-Propylbenzene and n-butylbenzene with further observations on ethylbenzene. Biochem. J. 64: 50-56.

Elovaara, E., K. Engstroem and H. Vainio. 1982. Unaltered metabolism of m-xylene in the presence of ethylbenzene. Dev. Biochem. 23: 265-268.

Engstrom, J. and R. Bjurstrom. 1978. Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. Scand. J. Work Environ. Health. 4: 195-203.

Faustov, A.S. 1958. Toxicity of aromatic hydrocarbons. I. Comparative toxicity of some aromatic hydrocarbons. II. Some problems of the toxic-hygiene properties of aromatic hydrocarbons. Tr. Voronezh. Gos. Med. Inst. 35: 247-255; 257-262. (Chem. Abstr. 54:25279d)

Faustov, A.S. 1960. Change of relative toxicity in a homologous series of benzene derivatives related to the mean of entrance into the organisms. Tr. Voronezh. Gos. Med. Inst. 36: 243-245. (Chem. Abstr. 57:10148c)

Faustov, A.S. and V.V. Kramsakov. 1968. Immunobiological reactivity of an organism during chronic poisoning with ethylbenzene and xylene. Tr. Voronezh. Gos. Med. Inst. 73(4): 41-46. (Chem. Abstr. 74:85860)

Fazzalari, F.A., Ed. 1978. Odor and Taste Threshold Values data, DS-48A. American Society for Testing and Materials, Philadelphia, PA. p. 71.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18: 219-232.

Gamberale, F., G. Annwall and M. Hultengren. 1978. Exposure to xylene and ethylbenzene. Scand. J. Work Environ. Health. 4: 204-211.

Gerarde, H.W. 1959. Toxicological studies on hydrocarbons. AMA Arch. Ind. Health. 19: 403-418.

Gut, I., J. Kopecky, J. Nerudova, M. Krivucova and L. Pelech. 1981. Metabolic and toxic interactions of benzene and acrylonitrile with organic solvents. Ind. Environ. Xenobiotics, Proc. Int. Conf. p. 255-262.

Hagemann, J. and J. Angerer. 1979. Biological monitoring in occupational ethylbenzene loading. Kolloq., Ber. Jahrestag. Dtsch. Ges. Arbeitsmed., 19th. p. 421-425. (Chem. Abstr. 94:196880)

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl.4): 66-75.

Holmberg, B., I. Jakobson and T. Malmfors. 1974. The effects of organic solvents on erythrocytes during hypotonic hemolysis. Environ. Res. 7: 193-205.

Ivanov, S.V. 1962a. Toxicology of ethylbenzene. Tr. Voronezh. Gos. Med. Inst. 47: 80-82. (Chem. Abstr. 61:3601b)

Ivanov, S.V. 1962b. Changes in blood due to chronic poisoning with ethylbenzene vapors. Tr. Voronezh. Gos. Med. Inst. 47: 83-85. (Chem. Abstr. 61:1163d)

Ivanov, S.V. 1964. Toxicology and hygienic rating of ethylbenzene content in the atmosphere of industrial areas. Gig. Tr. Prof. Zabol. 8(2): 9-14. (Chem. Abstr. 61:3607e)

Kaubisch, N., J.W. Daly and D.M. Jerina. 1972. Arene oxides as intermediates in the oxidative metabolism of aromatic compounds. Isomerization of methyl-substituted arene oxides. Biochemistry. 11(16): 3080-3088.

Kiese, M. and W. Lenk. 1973. w- and (w-1)-Hydroxylation of 4-chloropropionanilide by rabbits and rabbit liver microsomes. Biochem. Pharmacol. 22: 2565-2574.

Kiese, M. and W. Lenk. 1974. Hydroxyacetophenones: Urinary metabolites of ethylbenzene and acetophenone in the rabbit. Xenobiotica. 4(6): 337-343.

Lyman, W.J., W.F. Reehe and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York, NY. p. 960.

Mabey, W.R., J.H. Smith, R.T. Podoll et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. Monitoring and Data Support Div., Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Marks, T.A., T.A. Ledoux and J.A. Moore. 1982. Teratology of a commercial xylene mixture in the mouse. J. Toxicol. Environ. Health. 9(1): 97-106.

Maylin, G.A., M.J. Cooper and M.W. Anders. 1973. Effect of phenobarbital treatment on the stereochemistry of the in vitro metabolism of ethylbenzene. J. Med. Chem. 16(6): 606-610.

McMahon, R.E. and H.R. Sullivan. 1966. Microsomal hydroxylation of ethylbenzene. Stereospecificity and the effect of phenobarbital induction. Life Sci. 5: 921-926.

McMahon, R.E., H.R. Sullivan, J.C. Craig and W.E. Pereira, Jr. 1969. The microsomal oxygenation of ethylbenzene: Isotopic, stereochemical and induction studies. Arch. Biochem. Biophys. 132(2): 575-577.

Mihail, G., A. Zlavog, V. Anghelache and J. Bodnar. 1972. Serum ornithine carbamoyltransferase, test for evaluating hepatic alterations caused by some industrial toxic substances. Igiena. 21(5): 267-276. (Chem. Abstr. 79:1036)

Mill, T., W.R. Mabey, D.C. Bomberger et al. 1982. Laboratory Protocols for Evaluating the Fate of Organic Chemicals in Air and Water. Environmental Research Laboratory, ORD, U.S. EPA, Athens, GA. EPA 600/3-82-022.

NAS (National Academy of Sciences). 1977. Drinking Water and Health. Safe Drinking Water Committee, NAS, Washington, DC. p. 19-62.

NCI (National Cancer Institute). 1983. National Toxicology Program -- Toxicology Testing Program. Chemicals on Standard Protocol: Management Status. June 15, 1983.

Nestmann, E.R., E. G-H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.

Nielsen, G.D. and Y. Alarie. 1982. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Toxicol. Appl. Pharmacol. 65(3): 459-477.

Nunes, P. and P.E. Benville. 1979. Uptake and depuration of petroleum hydrocarbons in the Manila clam, Tapes semidecussata Reeve. Bull. Environ. Toxicol. 21: 719-726.

Patterson, J.W. and P.S. Kodukala. 1981. Biodegradation of hazardous organic pollutants. Chem. Eng. Pr. 77: 48-55.

Pokkrovskii, V.A. and R.I. Volchkova. 1968. Effect of some organic poisons on blood formation processes. Tr. Voronezh. Gos. Med. Inst. 73(4): 61-64. (Chem. Abstr. 74:97300)

Sandmeyer, E. 1981. Aromatic hydrocarbons: Ethylbenzenes. In: Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. 2B, G.D. Clayton and F.E. Clayton, Ed. p. 3256, 3303-3305.

Smith, J.N., R.H. Smithies and R.T. Williams. 1954a. The metabolism of alkylbenzenes. Stereochemical aspects of the biological hydroxylation of ethylbenzene to methylphenylcarbinol. Biochem. J. 56: 320-324.

Smith, J.N., R.H. Smithies and R.T. Williams. 1954b. The metabolism of alkylbenzenes. (a) Glucuronic acid excretion following the administration of alkylbenzenes. (b) Elimination of toluene in the expired air of rabbits. Biochem. J. 56: 317-320.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani and J.A. Striegel. 1962. Range-finding toxicity data. List VI. Am. Ind. Hyg. Assoc. J. 23: 95-107.

Sullivan, H.R., W.M. Miller and R.E. McMahon. 1976. Reaction pathways of in vivo stereoselective conversion of ethylbenzene to (-)mandelic acid. Xenobiotica. 6: 49-54.

Tabak, H.H., S.A. Quave, C-I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53: 1503-1518.

Toftgaard, R. and O.G. Nilsen. 1981. Induction of cytochrome P450 in rat liver after inhalation of aromatic organic solvents. Ind. Environ. Xenobiotics, Proc. Int. Conf. p. 307-317.

Toftgaard, R. and O.G. Nilsen. 1982. Effects of xylene and xylene isomers on cytochrome P450 and in vitro enzymatic activities in rat liver, kidney and lung. Toxicology. 23(2-3): 197-212.

Tsuruta, H. 1982. Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through the excised rat skin. Ind. Health. 20(4): 335-345.

U.S. EPA. 1980. Ambient Water Quality Criteria for Ethylbenzene. Office of Water Planning and Standards, Washington, DC. EPA 400/4-80-048. NTIS PB 81-117590.

Veith, G.D., D.L. Defoe and B.V. Bergstedt. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J. Fish Res. Board Can. 36: 1040-1048.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Company, NY. p. 628-630.

Vinokurova, M.I. 1970. Combined effect of styrene, butadiene and ethylbenzene on the functional indexes of the cardiovascular system. Tr. Azerb. Nauchno.-Issled. Inst. Gig. Tr. Prof. Zabol. 4: 21-26. (Chem. Abstr. 81:140347)

Williams, R.T. 1959. Detoxication mechanisms. In: The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds, 2nd ed. Champman and Hall Ltd., London. p. 197-204.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.